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(71) Applicant *(for all designated States except US)*: **7TM PHARMA A/S** [DK/DK]; Fremtidsvej 3, DK-2970 Hørsholm (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RECEVEUR, Jean-Marie** [FR/DK]; Lyøvej 30, 2. th, DK-2000 Frederiksberg (DK). **HÖGBERG, Thomas** [SE/SE]; Kabbarpsvägen 6, SE-232 52 Åkarp (SE). **LITTLE, Paul, Brian** [GB/DK]; Niels Brocks Gade 6, DK-1574 Copenhagen K (DK). **BJURLING, Anna, Emelie** [SE/SE]; Andréegatan 8, SE-211 40 Malmö (SE). **ELLING, Christian, E.** [DK/DK]; Viktoriagade 3, 1.th., DK-1655 Copenhagen V (DK). **NØRREGAARD, Pia, Karina** [DK/DK]; Johan Wilmannsvej 27, st tv, DK-2800 Kgs. Lyngby (DK).

(74) Agent: **ALBIHNS A/S**; H.C. Andersens Boulevard 49, DK-1553 Copenhagen (DK).

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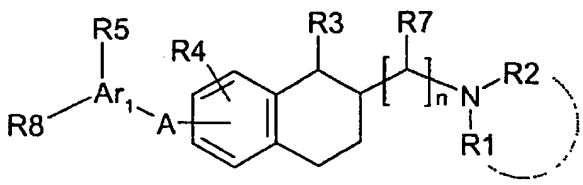
(54) Title: NOVEL AMINOTETRALINE COMPOUNDS FOR USE IN MCH RECEPTOR RELATED DISORDERS



(I)

(57) Abstract: Novel compounds of formula (I) which modulate MCH activity are disclosed in which A is a linker; Ar_1 is an aryl or heteroaryl group; R1 and R2 are hydrogen, straight or branched alkyl, alkenyl or alkynyl groups, cycloalkyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups and may be linked to each other; R3 is a hydrogen atom, Alk-, Alk-O-, hydroxy or keto group; R4 and R5 are hydrogen, halogen atoms, alkoxy groups, hydroxy, alkylamino groups, dialkylamino groups, hydroxylalkyl groups, carboxamido groups, acylamido groups, acyl groups, -CHO, nitrile, alkyl, alkenyl or alkynyl groups, $-CF_3$, $-OCF_3$, $-SCF_3$; $-SCH_3$, $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2Nalk_2$, $-SO_2Alk$; n is 1 or 2; R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, heteroaryloxyl groups, alkylheteroaryl groups, arylalkoxy groups, aryloxy groups, alkoxy groups, dialkylamino groups, -CONHAlk, -CONHAr, $-CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, $-SCH_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; or R8 is R6-Ar_2-B-; in which B is a connecting moiety; Ar_2 is an aryl or heteroaryl group; R6 is an R5 group; and which are useful in the treatment or prevention of *e.g.* obesity, depression, diabetes, bulimia etc.

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NOVEL AMINOTETRALINE COMPOUNDS FOR USE IN MCH RECEPTOR RELATED DISORDERS

Field of the invention

The present invention relates to novel compounds that interact with a melanin-concentrating hormone receptor, a MCH receptor. The compounds have modulating activity on the MCH receptor such as e.g. antagonistic, agonistic or allosteric activity and are useful for medicinal or cosmetic purposes such as, e.g. in the treatment or prevention of feeding disorders like obesity, metabolic syndrome, Type II diabetes, bulimina etc. or in the treatment or prevention of depression.

The invention also relates to therapeutic and/or prophylactic use of the compounds, to processes for the preparation of the novel compounds, to pharmaceutical compositions comprising the compounds, to the manufacture of such compositions and to methods for the treatment and/or prevention of MCH receptor related disorders.

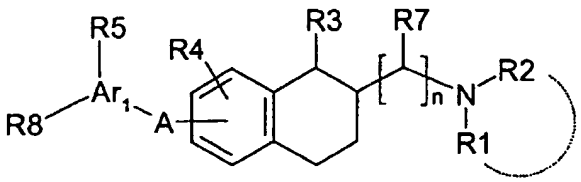
Background of the invention

Melanin-concentrating hormone (MCH) is a cyclic peptide that originally was isolated from salmoid pituitaries. In the fish, the 17 amino acid peptide causes aggregation of melanin and inhibits the release of ACTH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse and human exhibiting 100% amino acid identity. In the last decades there has been increasing activity in the research in the physiologic roles of MCH. It has been reported that MCH is involved in the feeding or body weight regulation, in energy balance, in response to stress, in water balance, in energy metabolism, in the general arousal/attention state, memory and cognitive functions and in psychiatric disorders. The biological effects of MCH are believed to be mediated by specific MCH receptors, and the MCH1 and MCH2 receptors have been described. Antagonists of MCH receptor (e.g. MCH1 receptor) may be suitable for use as obesity or weight reducing agents and they are also believed to have antidepressant and/or anxiolytic properties.

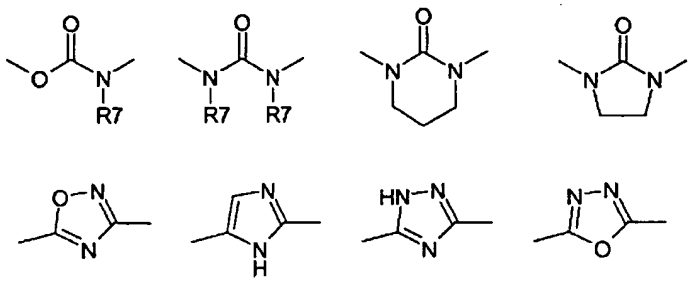
The present invention provides novel compounds that have a MCH modulating activity, i.e. antagonistic, inverse agonistic/negative antagonism, allosteric modulator, partial agonist or agonistic action.

Detailed description of the invention

The present invention relates to a compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of:



and, wherein the linker may be attached *via* either of the two free bonds to the Ar_1 group;

and R7 is the same or different and is hydrogen or a straight or branched C_1-C_6 alkyl or alkenyl group;

Ar_1 is an aryl or heteroaryl group such as, e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 and R2 are the same or different and selected from hydrogen, straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms, cycloalkyl groups with 3-7 carbon atoms, alkylcycloalkyl groups with 4-9 carbon atoms, alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine, alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, -$CONH_2$, -CONHAlk, $CONAlk_2$, aryl, substituted aryl, benzyl, or substituted benzyl groups;

R1 and R2 may optionally be linked to each other, when possible, as indicated in Formula I, and oxygen or nitrogen atoms may be inserted into the chain or ring in a chemically stable position,

both of R1 and R2 are preferably not hydrogen;

R3 is a hydrogen atom, Alk-, Alk-O-, hydroxy or keto group;

R4 and R5 may be the same or different selected from hydrogen, halogen atoms, alkoxy groups (Alk-O-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

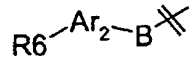
Alk is the same or a different alkyl, alkenyl or alkynyl group;

more than one R5 group, same or different, may be present on Ar_1; when more than one R5 group or one or more R5 and one R8 group are present they could be connected to each other to form rings;

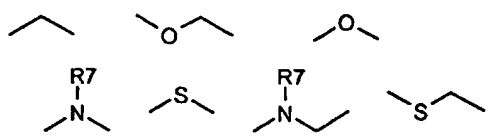
n is 1or 2;

R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, heteroaryloxyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr, -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -SCH_3, -CF_3, -OCF_3, -SCF_3

or R8 has the structure



in which B is a non-rigid connecting moiety selected from the group consisting of



which may be attached *via* either of the two free bonds to the Ar_1 group

and the -B- moiety is not placed *ortho*- to the -A- moiety;

Ar_2 is an aryl or heteroaryl group such as, *e.g.* phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R6 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

more than one R6 group, same or different, may be present on Ar_2; when more than one R6 group is present they could be connected to each other, directly or with a suitable connecting moiety, to form rings.

In the present context, the term "alkyl" is intended to indicate a branched or straight-chain, saturated chemical group containing 1-8 carbon atoms such as, e.g. 1-6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl *etc.*

The term "lower alkyl" is intended to indicate an alkyl group containing 1-6 carbon atoms, unless otherwise specified. Likewise, "lower alkenyl" and "lower alkynyl" are intended to indicate alkenyl and alkynyl groups, respectively containing 2-6 carbon atoms.

The term "alkenyl" is intended to indicate an unsaturated alkyl group having 2-8 carbon atoms and one or more double bonds.

The term "alkynyl" is intended to indicate an unsaturated alkyl group having 2-8 carbon atoms and one or more triple bonds.

The term "cycloalkyl" is intended to denote a cyclic, saturated alkyl group of 3-7 carbon atoms.

The term "cycloalkenyl" is intended to denote a cyclic, unsaturated alkyl group of 5-7 carbon atoms having one or more double bonds.

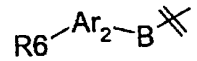
The term "alkoxy" is intended to indicate the group alkyl-O-.

The term "aryl" is intended to denote an aromatic (unsaturated), typically 6-membered, ring, which may be a single ring (e.g. phenyl) or fused with other 5- or 6-membered rings (e.g. naphthyl or indole).

The term "heteroaryl" is intended to denote an aromatic (unsaturated), 5- or 6-membered, ring, which may be a single ring (e.g. pyridyl) or fused with other 5- or 6-membered rings (e.g. quinoline or indole).

The term "heterocyclyl" is intended to indicate a cyclic unsaturated (heteroalkenyl), aromatic ("heteroaryl") or saturated ("heterocycloalkyl") group comprising at least one heteroatom.

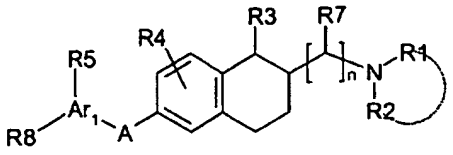
More specifically, the invention relates to a compound as described herein, wherein R8 has the structure



and B, Ar_2 and R6 are as defined in claim 1.

R8 may also be halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, heteroaryloxyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr, -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -SCH_3, -CF_3, -OCF_3, -SCF_3.

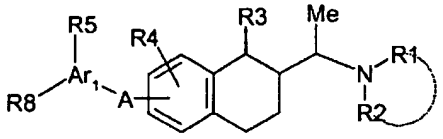
Other compounds according to the invention have the following structure (Formula Ia)



wherein Ar_1, A, R1, R2, R3, R4, R5, R7 and R8 are as defined above.

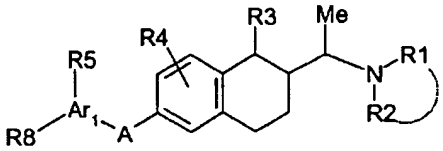
Furthermore, the invention relates to compounds described in Formula Ia, wherein n is 1 or wherein n is 1 and R7 is hydrogen.

The present invention also relates to compounds having the structure (Formula II):



and wherein Ar_1, A, R1, R2, R3, R4, R5 and R8 are as defined herein.

Additionally, compounds according to the invention may have the following structure (Formula IIa)

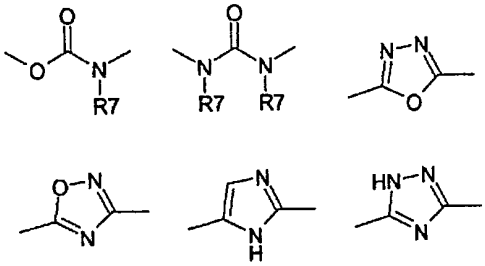


wherein Ar_1, A, R1, R2, R3, R4, R5 and R8 are as defined herein.

In one embodiment, Ar_1 is aryl or heteroaryl groups such as, *e.g.* phenyl, pyridine, and thiophene.

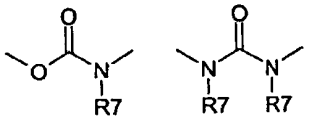
In another embodiment, R3 is hydrogen. Furthermore, R4 may be hydrogen. Additionally, R3 and R4 may both be hydrogen.

In specific embodiments, -A- is selected from the group consisting of:



and R7 is defined herein.

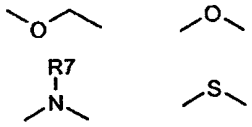
In yet another embodiment, -A- is selected from the group consisting of:



and R7 is defined herein.

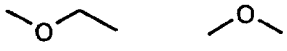
The compounds according to the present invention may be unsymmetrically substituted ureas, wherein at least one R7 on the connecting moiety A is not hydrogen.

In a compound according to the invention, B is selected from the group consisting of:

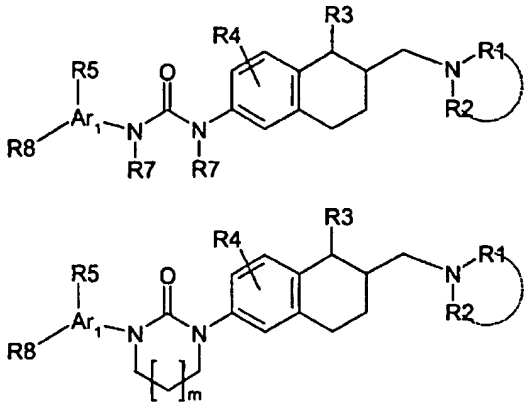


and R7 is as defined herein.

More specifically, B is selected from the group consisting of:



Other compounds according to the present invention have one of formulas



and one of R7 being hydrogen and m being 0 or 1

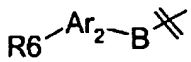
In an embodiment of the present invention, Ar_1 is an aryl, heterocyclyl or heteroaryl group such as phenyl, pyridine and thiophene, and n is 1.

In the structures given above, R3 may be hydrogen, R4 may be hydrogen or R3 and R4 may both be hydrogen.

The present invention includes compounds in which R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -$CONAlk_2$, -NHCO-Alk, -CO-Alk, -CF_3, -OCF_3, -SCF_3, -SCH_3.

Alternatively, R8 may be aryl groups (Ar), heterocyclyl groups, heteroaryl groups, alkylaryl groups, alkylheteroaryl groups, alkylheterocyclyl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), -CONHAr, -NHCO-Ar, or -CO-Ar.

In a compound according to the present invention, R8 has the structure



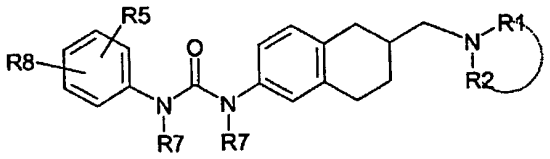
and Ar_1 and Ar_2 are the same or different aryl or heteroaryl groups such as phenyl, pyridine, and thiophene and n is 1.

When R8 has the structure given above, R3 may be hydrogen, R4 may be hydrogen or R3 and R4 may both be hydrogen.

In an embodiment of the present invention, R1 and R2 may be alkyl, alkenyl or cycloalkyl groups or joined in a morpholino, pyrrolidino or piperidino. Alternatively, R1 and R2 are H.

Additionally, in a compound according to the invention, Ar1 may be an aryl or heteroaryl group. Furthermore, Ar1 may be a phenyl group, Ar2 may be a phenyl group or both Ar1 and Ar2 may be phenyl groups.

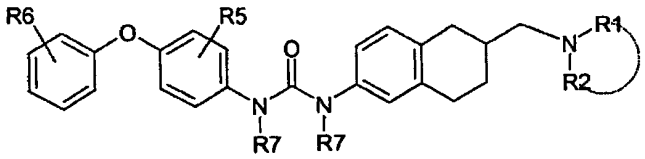
A further compound according to the invention may have the structure



and one of R7 being hydrogen.

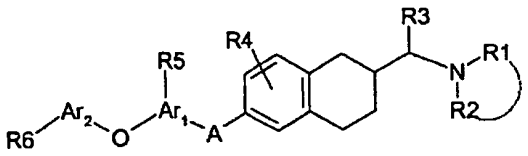
In a specific embodiment of the present invention, -B- is an ether linkage –O-.

The present invention also relates to compounds having the structure

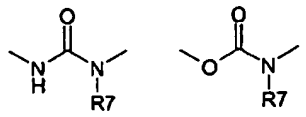


and one of R7 being hydrogen.

Additionally, the present invention also relates to compounds having the following structure



wherein –A- is a linker selected from



and R1, R2, R3, R4, R5, R6 and R7 are as defined in any of the preceding claims.

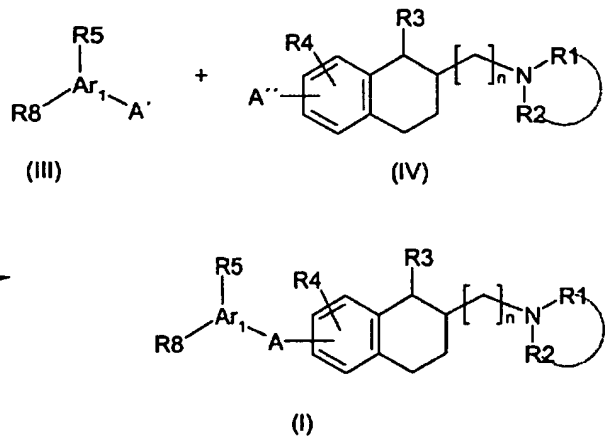
In this case, R3 may be hydrogen. Additionally, R1 and R3 may be hydrogen. Also, R1 and R2 may be hydrogen while R3 is methyl or R1 and R2 may be Alk. Additionally, Ar_1 and Ar_2 may be the same or different aryl or heteroaryl groups such as phenyl, pyridine, and thiophene. More specifically, Ar_1 and Ar_2 may be phenyl groups. Furthermore, R4 may be hydrogen.

In interesting embodiments, n together with R1 and R2 form a morpholino structure or a substituted morpholino group.

Other specific embodiments appear from the appended claims, description and the examples herein.

Synthetic routes

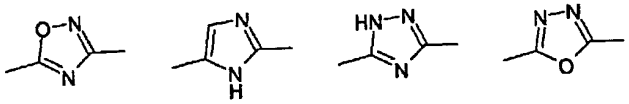
Compounds of Formula I are preferably made by connecting an appropriately functionalised (A'') tetraline moiety (IV) with a suitably functionalised (A') aryl moiety (III) using well-known synthetic routes according to the following general scheme:



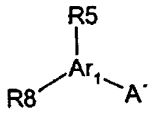
For example, urea bonds -A- can be formed by reaction of III having A' as isocyanate with IV having A'' equal to NHR7 using appropriate catalysis by base or acid. The reverse use of IV having A'' as isocyanate with III having A' equal to NHR7 can also be applied. Analogously, carbamates can for example be made by reaction of II having A' as

isocyanate with III having A'' equal to OH or the reverse use of OH and isocyanate in A' and A''.

The 5-membered heterocyclic linkers



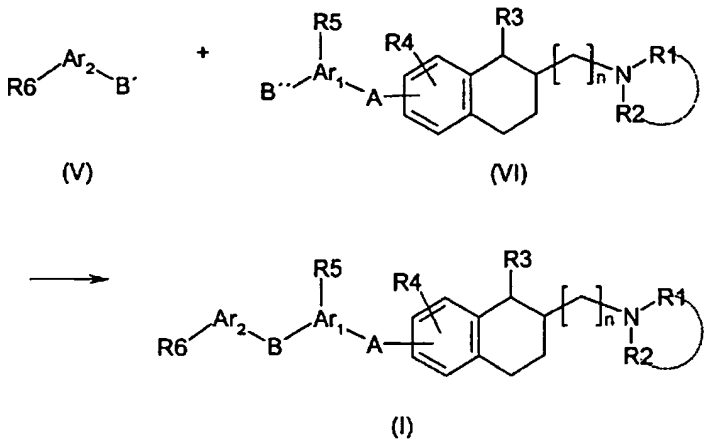
can be made according to standard cyclisation procedures using appropriate solvents, catalysts and temperatures. For example, formation of 1,2,4-triazole can be made from III with A' being acylhydrazide with IV with A'' being amide or thioamide or the reverse orientation of A' and A''. 1,2,4-Oxadiazole can be formed from III with A' being amidoxime with IV with A'' being carboxylic ester or the reverse orientation of A' and A''. 1,3,4-Oxadiazole can be formed from III with A' being acylhydrazide with IV with A'' being carboxylic ester or the reverse orientation of A' and A''.



(III)

Aromatic substituents R4, R5 and R8 are preferably introduced prior to formation of the A-linkage either direct or via a masked functionality that is compatible with the subsequent synthetic steps.

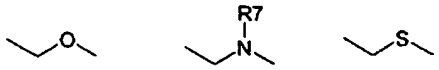
Alternatively, compounds of Formula I in which R8 is R6-Ar2-B- are made by connecting an appropriately functionalised (B'') arylated tetraline moiety (VI) with a suitably functionalised (B') aryl moiety (V) using well-known synthetic routes according to the following general scheme:



(V) (VI)

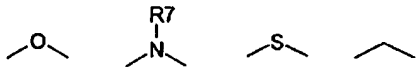
(I)

Formation of the connecting B-linkage to form



bonds in either direction between Ar_1 and Ar_2 can be carried out by N-, O- or S-alkylations of compounds V having B´ as OH, NH-R7, or SH with compounds VI having B´´ as CH_2-L, wherein L is a suitable leaving group such as halogen (Cl, Br, I), tosyl or mesyl using appropriate catalysts and conditions. The reverse use of B´ and B´´ in V and VI can be applied as well to form the linker in the opposite direction.

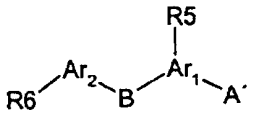
Formation of the connecting B-linkage to form



bonds can be carried out *via* coupling reactions of compounds V with B´ being OH, NH-R7, or SH with compound VI having B´´ as a suitable metal-reagent capable of forming the bond using appropriate catalysts and conditions or with B´´ being a halogen that can be replaced under thermal or metal-catalysed conditions. The reverse use of B´ and B´´ in V and VI can be applied as well. The $-CH_2-$ linkage may be obtained by reduction of the corresponding -CO- derivative.

Notably, the -B- linkage is normally introduced during the synthesis of intermediates III that are used in the coupling with IV. In most cases the –B- linkage is made in compounds

having A' groups that are compatible with the reaction conditions and that can be transformed into the required reactive moieties for subsequently forming the –A- linkage.

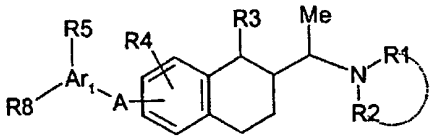


(III)

Aromatic substituents R4, R5 and R6 are preferably introduced prior to formation of the A- or B-linkage either direct or via a masked functionality that is compatible with the subsequent synthetic steps.

Alternatively, compounds of Formula I are made by N-alkylation of compounds of Formula I having R1 and R2 being hydrogen using well-known synthetic routes such as reductive alkylation or alkylation with alkyl halides in case the functionalisation of the molecule is compatible with this type of reactions.

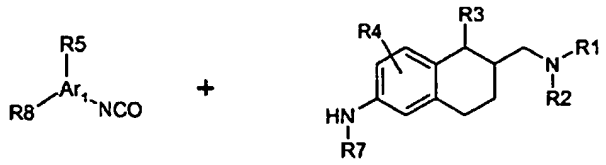
Compounds corresponding to Formula II are made in an analogous way as described for compounds of Formula I.



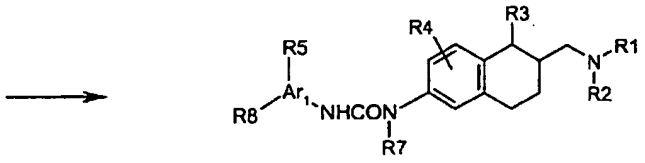
(II)

Synthetic method 1A

Thus, compound (IIc) having NHCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.



(IIIa) (IVa)



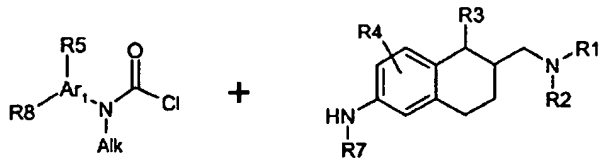
(IIc)

Compound IIIa and an excess of compound IVa are reacted in an inert solvent in accordance with standard procedures. Typically, inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. Reaction temperature is usually room temperature and the reaction time is 2 hours to 1 day.

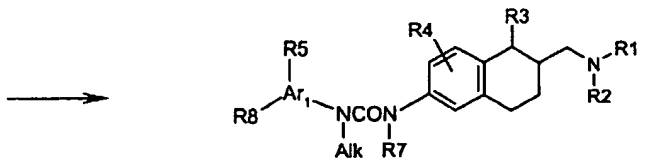
Compound IIIa can be produced from the corresponding carboxylic acid. For instance, 4-phenoxyphenylisocyanate can be produced in accordance with methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley); R.C. Larock.

Synthetic method 1B

Compound IId having N-AlkCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.



(IIIb) (IVa)



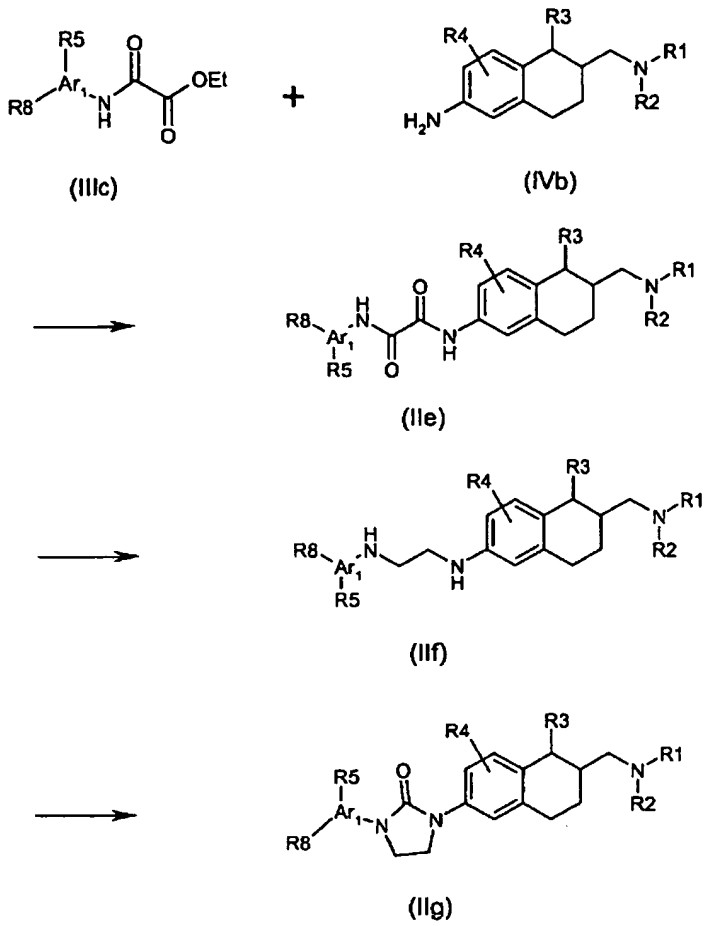
(IId)

Compound IVa and 1 equivalent of compound IIIb are reacted in an inert solvent in the presence of an excess of a base in accordance with known procedures (e.g. WO 9205174; *J. Med. Chem.* 43(20), 3653-3664, 2000). Suitable inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. Triethylamine, diisopropylethylamine or sodium carbonate can be used as a base, for instance. Typically, the reaction temperature is 0 °C to room temperature and the reaction time is 1 hour to 1 day.

Compound IIIb can be produced from the corresponding N-alkyl aromatic amine by well-known methods. For instance, N-methyl-N-4-phenoxyphenylcarbamoyl chloride can be produced in accordance with methods such as described in *J. Labelled Compd. Radiopharm.* 29(2),149-155, 1991.

Synthetic method 1C

Compound IIg having 5-membered ring urea as linker A can be produced, for instance, by the following reaction sequence.



(IIIc) (IVb)

(IIe)

(IIf)

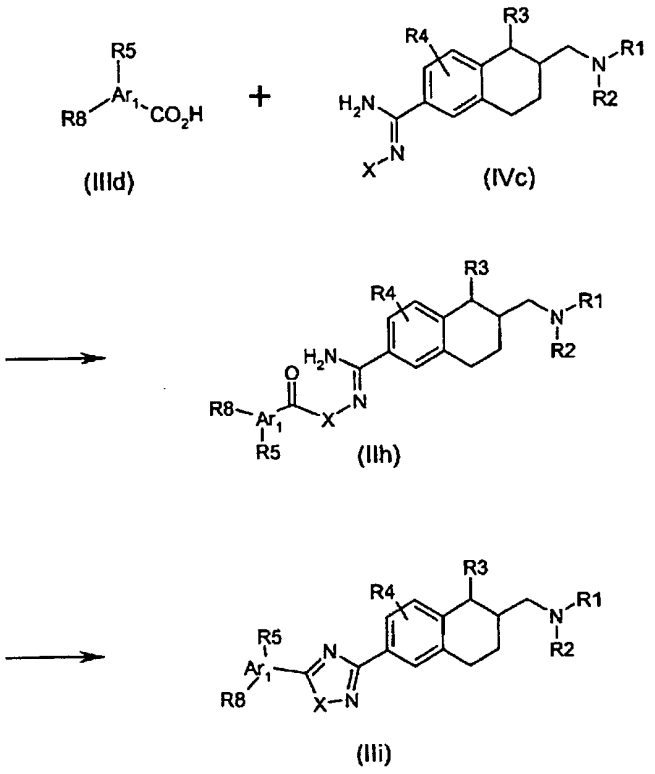
(IIg)

Compound IIf and 1 equivalent of carbonyldiimidazole are reacted in an inert solvent at elevated temperature until the reaction is completed. Typically, the reaction is conducted at reflux in acetonitrile for less than 24 hours.

Compounds IIIc, IIe and IIf can be produced following the functional group conversions described in procedures as described in *J.Med.Chem.* 43(20), 3653-3664, 2000.

Synthetic method 2

Compound Ii having 1,2,4-oxadiazole (X=O) or 1,2,4-triazole (X=NH) heterocyclic rings as linker A can be produced, for instance, by the following cyclodehydratation reaction.



Compound IIh is reacted in an inert solvent with or without the presence of a suitable base or acid (e.g. N-tetrabutyl ammonium fluoride, sodium hydride, sodium ethoxide or polyphosphoric acid) in accordance with standard methods such as described in *Tetrahedron Lett.* 42, 1441-1443, 2001; *Tetrahedron Lett.* 42, 1495-1498, 2001. Suitable, inert solvents can be ether solvents, amide solvents and aromatic solvents. The reaction temperature is usually room temperature to 100°C and the reaction time is 1 hour to 3 days.

Compound IIh can be produced by reacting an activated derivative of compound IIId with 1 equivalent of compound IVc in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine and sodium carbonate.

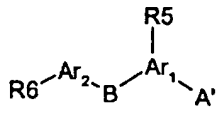
Appropriate examples of the activated derivatives of compound IIId include active esters (e.g. esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzo-triazole, N-hydroxysuccinamide), acid chlorides, symmetrical or unsymmetrical anhydrides

and orthoesters. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Compound IVc can be produced from the corresponding amino compound IVb by well known methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock; In "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky).

Synthetic method 3

Compound III



(III)

wherein A´ being groups that are compatible with the reaction conditions and that can be transformed into the required reactive moieties for subsequently forming the -A- linkage (e.g. –NCO and -NAlkCOCl) can be produced by firstly connecting Ar1 to Ar2 to each other in accordance with standard methods including N-, O-, and S-alkylations and metal-catalysed cross couplings. One or several aromatic substituents R5 and R6, depending on their chemical properties, can be introduced either before or after the connection of Ar1 and Ar2 to each other.

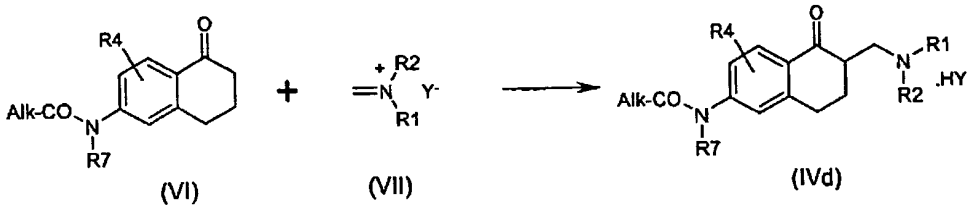
Compounds III with B = -O-, -NR7-, or -S- are prepared from a suitable aryl halide and the corresponding phenol, aniline or thiol by heating with for example NaH or K_2CO_3 as base with the presence of a copper salt in DMF, pyridine or other high boiling solvents. An example of a metal assisted preparation of diaryl ethers is the coupling of a phenol with an arylbromide in the presence of $Pd(OAc)_2$ together with a phosphine ligand and K_3PO_4. For instance, 4-(4-chloro-phenoxy)benzoic acid can be produced in a two-steps synthesis from the corresponding 4-fluoro-acetophenone and 4-chlorophenol in accordance with methods such as described in *Synthesis*, 63-68, 1991 and *Eur. J. Med. Chem.*, 3, 205-214, 1984.

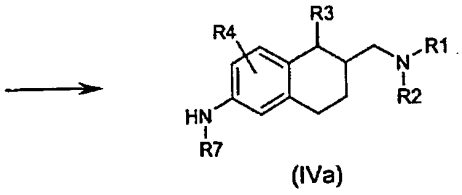
For compounds III with B equal to $-CH_2O-$ the preparation is performed by heating a benzyl halide and phenol with K_2CO_3 or NaOMe as base. These ethers can also be prepared from suitable benzyl alcohols and phenols utilising Mitsunobu conditions (DEAD and PPh3). Compounds III with B equal to $-CH_2NR7-$ can be prepared from an aniline and

a benzyl halide using K_2CO_3 as base. The corresponding thioether can be formed from a benzyl halide and thiophenol using KOH or NaOMe as bases and with for example ethanol as the solvent.

Synthetic method 4

Compound IVa can be prepared by Mannich type reactions from the corresponding protected tetralone, preferably using a preformed iminium ion as outlined in the following route. Y^- being a suitable organic or inorganic counter anion such as, e.g., Cl^-, Br^-, I^-, ClO_4^- or CF_3COO^-.



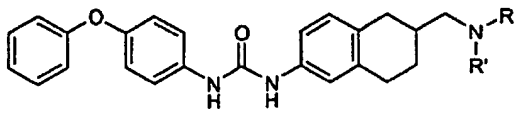


Tetralone VI and a slight excess of iminium ion VII are reacted in an inert solvent at elevated temperature to yield compound IVd. Typically, the reaction is conducted at reflux in acetonitrile for less than 5 hours. Conversion of compound IVd into compound IVa can be achieved in accordance with standard procedures such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock.

Below follow some examples of specific compounds according to the invention. In the compounds mentioned, one part of the molecule such as e.g. the amine group, the linker –A-, the linker –B-, the Ar_1 or Ar_2 group, the R4, R5, R6 group or the chain length is varied, while the other parts are conserved. Though not shown nor specifically mentioned, the invention also includes all compounds wherein all variations in one part of the molecule, e.g. linker –A- is combined with all variations in another of the features, e.g. variation in the Ar_1 group.

Amine modifications

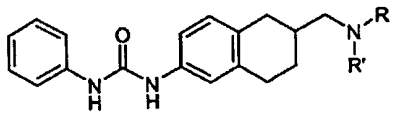
Examples with variations in the amine group based on the following structure are:



1-(6-Diethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dipropylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dibutylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-{6-[(Ethyl-methyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-{6-[(Methyl-propyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-{6-[(Butyl-methyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-{6-[(Ethyl-propyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-(4-Phenoxy-phenyl)-3-(6-piperidin-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(4-Phenoxy-phenyl)-3-(6-pyrrolidin-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Morpholin-4-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-[6-(4-Methyl-piperazin-1-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea,
1-[6-(4-Benzyl-piperazin-1-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea,
1-(4-Phenoxy-phenyl)-3-[6-(4-phenyl-piperidin-1-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-urea,
N-[3-(1-{6-[3-(4-Phenoxy-phenyl)-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-phenyl]-acetamide,
1-{6-[4-(3-Methoxy-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-{6-[4-(3-Hydroxy-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-{6-[4-(3-Cyano-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,

1-{6-[4-(3-Methylamino-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
1-{6-[4-(3-Dimethylamino-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-(4-phenoxy-phenyl)-urea,
3-(1-{6-[3-(4-Phenoxy-phenyl)-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-benzamide,
N-Methyl-3-(1-{6-[3-(4-phenoxy-phenyl)-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-benzamide,
N,N-Dimethyl-3-(1-{6-[3-(4-phenoxy-phenyl)-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-benzamide,

Examples with variations in the amine group based on the following structure are:



1-(6-Diethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dipropylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dibutylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-{6-[(Ethyl-methyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,
1-{6-[(Methyl-propyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,
1-{6-[(Butyl-methyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,
1-{6-[(Ethyl-propyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,
1-phenyl-3-(6-piperidin-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-phenyl-3-(6-pyrrolidin-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea, 1-(6-Morpholin-4-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea, 1-[6-(4-Methyl-piperazin-1-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-phenyl-urea,
1-[6-(4-Benzyl-piperazin-1-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-phenyl-urea,
1-phenyl-3-[6-(4-phenyl-piperidin-1-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-urea,
N-[3-(1-{6-[3-phenyl-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-phenyl]-acetamide,
1-{6-[4-(3-Methoxy-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,
1-{6-[4-(3-Hydroxy-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,

1-{6-[4-(3-Cyano-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,

1-{6-[4-(3-Methylamino-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,

1-{6-[4-(3-Dimethylamino-phenyl)-piperidin-1-ylmethyl]-5,6,7,8-tetrahydro-naphthalen-2-yl}-3-phenyl-urea,

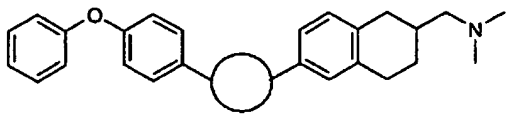
3-(1-{6-[3-phenyl-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-benzamide,

N-Methyl-3-(1-{6-[3-phenyl-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-benzamide,

N,N-Dimethyl-3-(1-{6-[3-phenyl-ureido]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-piperidin-4-yl)-benzamide,

Linker A modifications

Examples of some of the different compounds with variations of the linker –A- based on the following structure are:



1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1-methyl-3-(4-phenoxy-phenyl)-urea,

3-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1-methyl-1-(4-phenoxy-phenyl)-urea,

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-imidazolidin-2-one,

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-tetrahydro-pyrimidin-2-one,

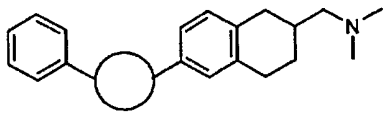
Dimethyl-{6-[5-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,

Dimethyl-{6-[3-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,

Dimethyl-{6-[5-(4-phenoxy-phenyl)-4*H*-imidazol-2-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,

Dimethyl-{6-[2-(4-phenoxy-phenyl)-2*H*-imidazol-4-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[5-(4-phenoxy-phenyl)-1*H*-[1,2,4]triazol-3-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine.

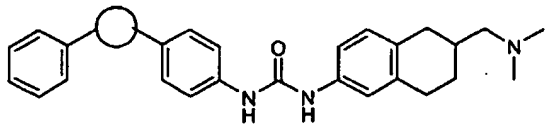
Examples with variations of the linker –A- based on the following structure are:



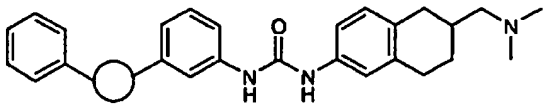
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1-methyl-3-phenyl-urea,
3-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1-methyl-1-phenyl-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-imidazolidin-2-one,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-tetrahydro-pyrimidin-2-one,
Dimethyl-{6-[5-phenyl-[1,2,4]oxadiazol-3-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[3-phenyl-[1,2,4]oxadiazol-5-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[5-phenyl-4*H*-imidazol-2-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[2-phenyl-2*H*-imidazol-4-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[5-phenyl-1*H*-[1,2,4]triazol-3-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine,
Dimethyl-{6-[5-phenyl-[1,3,4]oxadiazol-2-yl]-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl}-amine.

Linker B modifications

Examples of some compounds with variations of the linker -B- based on the following structure are:



1-(4-Benzyl-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenylsulfanyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenylamino-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(methyl-phenyl-amino)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxymethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenylsulfanylmethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenylaminomethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-{4-[(methyl-phenyl-amino)-methyl]-phenyl}-urea,
1-(4-Benzyloxy-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(4-Benzylsulfanyl-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(4-Benzylamino-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-[4-(Benzyl-methyl-amino)-phenyl]-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,

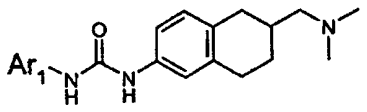


1-(3-Benzyl-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-phenylsulfanyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-phenylamino-phenyl)-urea,

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[3-(methyl-phenyl-amino)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-phenoxymethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-phenylsulfanylmethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-phenylaminomethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-{3-[(methyl-phenyl-amino)-methyl]-phenyl}-urea,
1-(3-Benzyloxy-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(3-Benzylsulfanyl-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(3-Benzylamino-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-[3-(Benzyl-methyl-amino)-phenyl]-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea.

Ar_1 modifications

Examples with variations in the Ar1 group based on the following structure are:

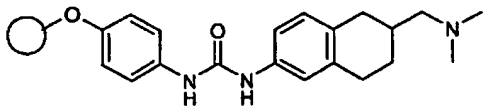


1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyridin-4-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-pyridyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[5-indolyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyrimidinyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyrimidin-5-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[2-pyrazinyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[2-thiophenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[3-isoxazolyl]-urea.

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(5-benzofuranyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(8-quinolinyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-thiophen-3-yl)-urea.

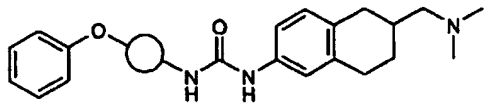
Ar_1 and Ar_2 modifications

Examples with variations in the Ar2 groups based on the following structure are:



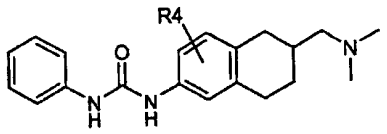
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyridin-4-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyridin-3-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyridin-3-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyrimidin-4-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyrimidin-5-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(pyrazin-2-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(thiophen-2-yloxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(isoxazol-3-yloxy)-phenyl]-urea.

Examples with variations in the Ar_1 group based on the following structure are:



1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(5-phenoxy-pyridin-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(6-phenoxy-pyridin-3-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-thiophen-3-yl)-urea.

R4, R5 and R8 modifications

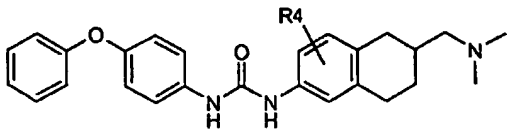


Examples of compounds with different R4 groups, which could be present in any of the three positions, are:

1-(6-Dimethylaminomethyl-1-fluoro-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(3-Chloro-6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(4-Bromo-6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-3-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-3-methylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(4-Dimethylamino-6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-1-hydroxymethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-1-(*N*-methyl-carboxamido)-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-4-carboxamido-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-3-(*N*,*N*-dimethyl-carboxamido)-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-4-acetamido-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-4-methyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-3-trifluoromethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,

1-(6-Dimethylaminomethyl-4-trifluoromethoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea,
1-(6-Dimethylaminomethyl-1-dimetylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-phenyl-urea

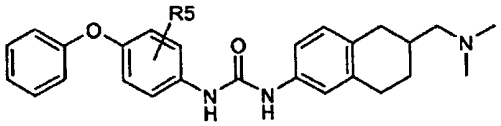
R4, R5 and R6 modifications



Examples of compounds with different R4 groups, which could be present in any of the three positions, are:

1-(6-Dimethylaminomethyl-1-fluoro-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(3-Chloro-6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(4-Bromo-6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-3-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-3-methylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(4-Dimethylamino-6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-1-hydroxymethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-1-(*N*-methyl-carboxamido)-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-4-carboxamido-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-3-(*N*,*N*-dimethyl-carboxamido)-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,

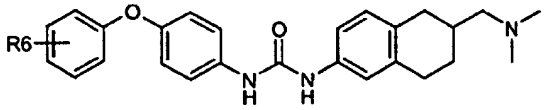
1-(6-Dimethylaminomethyl-4-acetamido-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-4-methyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-3-trifluoromethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-4-trifluoromethoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-1-dimetylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea



Examples of compounds with different R5 groups, which could be present as one or more substituents in any of the positions, are:

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(2-fluoro-4-phenoxy-phenyl)-urea,
1-(3-Chloro-4-phenoxy-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(3-Bromo-6-methoxy-4-phenoxy-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-bromo-2-hydroxy-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-methoxy-2-fluoro-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-methylamino-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-dimethylamino-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-hydroxymethyl-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-carboxamido-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(2-(*N*-methyl-carboxamido) -4-phenoxy-phenyl)-urea,

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-(*N,N*-dimethyl-carboxamido) -4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-(acetamido) -4-phenoxy-phenyl)-urea,
1-(2-Cyano-3-chloro-4-phenoxy-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-methyl-4-phenoxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-2-trifluoromethyl-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-3-trifluoromethoxy-phenyl)-urea.

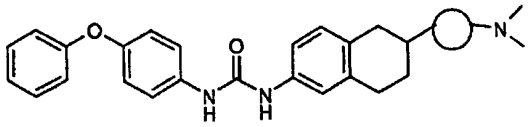


Examples of compounds with different R6 groups, which could be present as one or more substituents in any of the positions, are:

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-fluoro-phenoxy)-phenyl]-urea,
1-[4-(4-Flouro-3-chloro-phenoxy)-phenyl]-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-[4-(4-Bromo-3-trifluoromethoxy-phenoxy)-phenyl]-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(3,4-methylenedioxy-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-methoxy-3-fluoro-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-methylamino-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-dimethylamino-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(3-hydroxymethyl-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-(*N,N*-dimetylcarboxamido)-phenoxy)-phenyl]-urea,

1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(3-carboxamido-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-acetamido-phenoxy)-phenyl]-urea,
1-[4-(4-Cyano-3-chloro-phenoxy)-phenyl]-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-*p*-tolyloxy-phenyl)-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-trifluoromethyl-phenoxy)-phenyl]-urea,
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(4-trifluoromethoxy-phenoxy)-phenyl]-urea

Side chain modifications



Example of such compounds are
1-[6-(Dimethylaminomethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea,
1-[6-(2-Dimethylamino-1-ethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea,
1-[6-(1-Dimethylamino-1-ethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea,
1-[6-(1-Dimethylamino-2-propyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea,
1-[6-(2-Dimethylamino-1-propyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea.

Salts, complexes or solvates

The invention also relates to physiologically acceptable salts, complexes, solvates or prodrugs of the compounds of the invention.

When a compound of the invention possesses a basic functional group it can form a salt with an inorganic or organic acid.

Examples of physiologically acceptable salts of the compounds according to the invention include salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid (to form e.g. a nitrate or a nitrite), sulfuric acid (to form e.g., a H_2SO_3 salt, a sulfate or a H_2SO_5 salt) and phosphoric acid (to form e.g. a H_3PO_3 salt or a H_3PO_4 salt)

Examples of salts with organic acids include salts with formic acid, acetic acid, propionic acid, butyric acid, pentanoic acid, oxalic acid, tartaric acid, malonic acid, succinic acid, citric acid, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, acrylic acid, malic acid, fumaric acid, H_2CO_3, lactic acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 3-chlorobenzoic acid.

Examples of salts with acidic amino acids include salts with aspartic acid and glutamic acid.

Optical isomers

When a compound of the invention contains optical isomers, diastereomers or other stereroisomers these are included as a compound of the invention as well as the racemate, i.e. mixture of enantiomers. Each of them can be obtained by methods known by a person skilled in the art. For example the optical isomer can be obtained using an optically active synthetic intermediate, an asymmetric synthesis or subjecting the racemic mixture of the final product or a suitable intermediate to optical resolution in accordance with known methods such as, e.g., fractional recrystallisation method, chiral column method, diastereomer method etc.

Other forms

The invention also encompasses a compound in amorphous, any polymorphous or any crystalline form.

Disorders

The compounds according to the invention can be used in medicine and modulate the activity of a MCH receptor. The compounds may be used as agents for preventing or treating diseases caused by or involving a melanin-concentrating hormone, i.e. they are useful for treating or preventing a MCH or MCH receptor related disorder or abnormality in a subject such as, e.g., an animal or a mammal such as, e.g., a human.

The compounds according to the invention may have antagonistic, inverse agonistic, agonistic or allosteric activity against a MCH receptor, normally antagonistic activity.

In the present context an agonist is defined as a compound that increases the functional activity of a MCH receptor (e.g. the signal transduction through a receptor). The term "agonist" includes partial agonist, i.e. which increases the functional activity of the receptor to a submaximal level. An inverse agonist (or negative antagonist) is defined as a compound that decreases the basal functional activity of a MCH receptor. An allosteric compound is defined as a compound that enhances or diminishes the effects of other receptor ligands.

An antagonist is defined as a compound that decreases the functional activity of a MCH receptor either by inhibiting the action of an agonist or by its own intrinsic activity.

The MCH receptors mentioned in the invention include MCH1 and MCH2 receptors. It also includes MCH receptors comprising the amino acid sequence CTLITAMDAN or CTIITSLDTC. It also includes MCH receptors having at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequences CTLITAMDAN or CTIITSLDTC.

The MCH receptors may be an animal or a mammalian or non-mammalian receptor, such as a human receptor.

Increasing or decreasing the activity of a MCH receptor such as, e.g. a MCH1 receptor alleviates a MCH-related disorder or abnormality. In specific embodiments the disorder is a steroid or pituitary hormone disorder, an epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, a muscoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as, e.g., Alzheimer's disease, a sensory modulation and transmission disorder, a motor

coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder such as, e.g. Parkinson's disease, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder such as, e.g. depression, a stress-related disorder, a fluid-balance disorder, a urinary disorder such as, e.g., urinary incontinence, a seizure disorder, pain, psychotic behaviour such as, e.g., schizophrenia, morphine or opioid tolerance, opiate addiction or migraine.

More specifically, the compounds of the invention are useful for the treatment or prevention of feeding disorders such as, e.g., overweight, adiposity, obesity and bulimia (e.g. malignant mastocytosis, exogeneous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophyseal adposity, hypoplasmic obesity, hypophysal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity etc.), hyperfagia, emotional disorders, dementia or hormonal disorders.

In the present context the term body mass index or BMI is defined as body weight (kg)/height^2 (m^2), and the term overweight is intended to indicate a BMI in a range from about 25 to about 29.9, whereas obesity is intended to indicate a BMI, which is at least about 30. The compounds of the present invention are useful as agents for reducing body mass.

A compound of the invention is also useful as an agent for preventing or treating lifestyle diseases such as, e.g., diabetes, diabetic complications (e.g. retinopathy, neuropathy, nephropathy etc.), arteriosclerosis and gonitis.

The present invention further relates to a cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to the invention

The invention also relates to a method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A mentioned above, the MCH-related disorders may be a feeding disorder. Accordingly, the invention relates to a method for the treatment and/or prophylaxis of diseases caused

by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

The invention also relates to a method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Furthermore, the invention relates to a method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Another aspect of the invention is a method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A still further aspect of the invention is a method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Pharmaceutical compositions

The compounds for use in the methods according to the invention are normally presented in the form of a pharmaceutical or a cosmetic composition comprising the specific compound or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

The compounds may be administered to the animal including a mammal such as, e.g., a human by any convenient administration route such as, e.g., the oral, buccal, nasal, ocular, pulmonary, topical, transdermal, vaginal, rectal, ocular, parenteral (including *inter alia* subcutaneous, intramuscular, and intravenous), route in a dose that is effective for the individual purposes. A person skilled in the art will know how to chose a suitable administration route.

The pharmaceutical or cosmetic composition comprising a compound according to the invention may be in the form of a solid, semi-solid or fluid composition.

The solid composition may be in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, granulates, particulate material, solid dispersions or solid solutions.

A semi-solid form of the composition may be a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or a aerosol.

Fluid compositions, which are sterile solutions or dispersions can utilized by for example intraveneous, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection of infusion. The compounds may also be prepared as a sterile solid composition, which may be dissolved or dispersed before or at the time of administration using e.g. sterile water, saline or other appropriate sterile injectable medium.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be vagitories, suppositories, plasters, patches, tablets, capsules, sachets, troches, devices etc.

The dosage form may be designed to release the compound freely or in a controlled manner e.g. with respect to tablets by suitable coatings.

The pharmaceutical composition may comprise a therapeutically effective amount of a compound according to the invention.

The content of a compound of the invention in a pharmaceutical composition of the invention is e.g. from about 0.1 to about 100% w/w of the pharmaceutical composition.

The pharmaceutical or cosmetic compositions may be prepared by any of the method well known to a person skilled in pharmaceutical or cosmetic formulation.

In pharmaceutical or cosmetic compositions, the compounds are normally combined with a pharmaceutical excipient, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically or cosmetically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavours, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Dosage

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the composition, the route of administration, the frequency of administration, the age, weight, gender, diet and condition of the subject to be treated and the condition being treated and the advancement of the disease condition etc.

Suitable dosages may be from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

The amounts can be divided into one or several doses for administration daily, every second day, weekly, every two weeks, monthly or with any other suitable frequency. Normally, the administration is daily.

A compound or a pharmaceutical composition according to the invention may be used in combination with other drug substances such as agents for treating disorders like e.g. diabetes, diabetes complications, obesity, hypertension, hyperlipidemia, arteriosclerosis, arthritis, anxiety, and/or depression etc.

5

Experimental

Materials and methods

Transfections and Tissue Culture - The cDNA encoding the human MCH-1 receptor was cloned from a human brain cDNA library and cloned into the eukaryotic expression vector pcDNA3.1 (Invitrogen). Assays were performed on transiently transfected COS-7 cells or stably transfected CHO (Chinese Hamster Ovary) cells, expressing the human MCH-1 receptor in pcDNA3.1. Stable MCH-1 receptor transfectants of CHO cells were obtained using 5 μg plasmid cDNA and a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) with subsequent selection in 1 mg/ml G418 (Life Technology). Clones were screened by a MCH receptor radioligand binding assay (as described below). Stably transfected CHO cells were maintained in RPMI 1640 culture medium (Invitrogen), supplemented with 10 % fetal calf serum (Invitrogen), 100 U/ml penicillin, 100 μg/ml streptomycin (Life Technology), and 500 μg/ml G418 (Life Technology). COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 (Invitrogen) supplemented with 10 % fetal calf serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and were transiently transfected by a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) two days before assay.

Radioligand Binding Assay -Transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor were seeded in multi-well culture plates one day before the assay. The number of cells per well was determined by the apparent expression efficiency of the cell line aiming at 5 - 10 % binding of the added radioligand. Cells were assayed by competition binding for 3 hours at room temperature using 15 pM [^{125}I]-MCH (Amersham Pharmacia Biotech) plus variable amounts of unlabeled ligand in 0.5 ml of a 25 mM Hepes buffer, pH 7.4, supplemented with 10 mM $MgCl_2$, 5 mM $MnCl_2$, 10 mM NaCl, 0.1 % (w/v) bovine serum albumin (BSA), 100 μg/ml bacitracin. The assay was performed in duplicate. Nonspecific binding was determined as the binding in the presence of 1 μM MCH (Bachem). Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the dissociation and inhibition constants (K_d and K_i) were estimated from competition binding using the equations $K_d=IC_{50}-L$ and $K_i=IC_{50}/(1+L/K_d)$, respectively, where L is the concentration of radioligand.

Phosphatidylinositol assay - To assay phosphatidylinositol turnover, transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor ($2x10^5$ cells/well) were incubated for 24 h with 5 μCi of [^{3}H]-*myo*-inositol (Amersham Pharmacia Biotech) in 0.5 ml inositol-free culture medium. Cells were washed twice in PI-buffer: 20 mM HEPES, pH 7.4, supplemented with 140 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 1 mM $CaCl_2$, 10 mM glucose, 0.02% (w/v) bovine serum; and were incubated in 0.5 ml PI-buffer supplemented with 10 mM LiCl at 37 ^{0}C for 45 min. Phosphatidylinositol turnover was stimulated by submaximal concentrations of MCH, i.e. 10 nM in the presence of increasing amounts of ligand. The ligand was added 5 min. before adding the agonist (MCH). Cells were extracted with 10 mM ice-cold Formic acid, and the generated [^{3}H]-inositol phosphates were purified on Bio-Rad AG 1-X8 anion-exchange resin. Determinations were made in duplicate. PI data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego).

Scintillation Proximity Assay (SPA)– Measurement of [^{125}I]-MCHbinding was performed in duplicates by incubating membranes and beads with tracer in the presences of various concentrations of test compounds (10^{-8} to 10^{-4} M) in DMSO (3 µl) at room temperature for two hours. Membranes and beads were pre-incubated for 20 min. The binding buffer contained 50 mM Tris (pH 7.4), 8 mM MgCl2, 12% glycerol, 0.1% (w/v) bovine serum albumin (BSA), and protease inhibitors (Complete protease inhibitor cocktail tablets, Roche). A final [^{125}I]-MCH(2000 Ci/mmol; Amersham Pharmacia Biotech) concentration of 75.000 cpm/well (33.8 nCi) was applied and PEI-treated WGA-coupled PVT SPA beads, type B from Amersham Pharmacia Biotech were used at a final concentration of 0.4 mg/well. Moreover, CHO-K1 membranes expressing the hMCHreceptor were purchased from Euroscreen (ES-370-M) and a final concentration of 2µg/well were used. Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the inhibition constant (K_i) were estimated from competition binding using the equation $K_i=IC_{50}/(-1+L/K_d)$, where L and K_d are the concentration and affinity constant, respectively, of the radioligand.

In Vivo model measuring effects on food intake - The effects of test compounds on food intake were studied in male Sprague Dawley rats (290 – 325 g). The animals were individually housed in plexiglas cages (370 cm^2) at room temperature (21 ± 2 °C)and maintained on a 12 : 12h light – dark cycle (08.00 h – 20.00 h dark). They had free access to water; food (normal rat chow) was only available for the first 6 h of the dark

period. The actual experiments studying food intake were conducted when the animals were well accustomed to the housing conditions and feeding paradigm. At least a 10 – day acclimatization period was observed after entrance of the animals in the facilities.

At a day of an experiment, weight matched groups (n = 6-7) were injected with one of the test compounds (i.p. 10 mg/kg, dissolved in 10 % Tween 80), or the solvent (10 % Tween 80, 2 ml/kg). Cumulative food intake was registered over the 6-h feeding period. Results were analyzed by one-way ANOVA followed by post hoc Bonferroni test.

References:

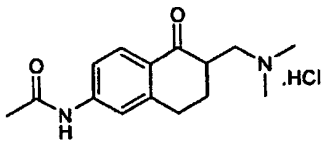
Gether, U., Marray, T., Schwartz, T.W., and Johansen, T.E. (1992). Stable expression of high affinity NK_1 (substance P) and NK_2 (neurokinin A) receptors but low affinity NK_3 (neurokinin B) receptors in transfected CHO cells. *FEBS Lett.*, 296, 241-244.

Johansen, T.E., Schøller, M.S., Tolstoy, S. and Schwartz, T.W. (1990). Biosynthesis of peptide precursors and protease inhibitors using new constitutive and inducible eukaryotic expressions vectors. *FEBS Lett.*, 267, 289-294.

Examples

Example 1

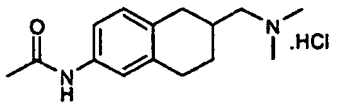
***N*-(6-Dimethylaminomethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide; hydrochloride**



To a solution of 6-acetamidotetralone (3.9 g, 19.2 mmol) in dry acetonitrile (80 ml) was quickly added, under an argon atmosphere, N-N-dimethylmethyleneiminium chloride (2.15 g, 23 mmol). The reaction mixture was stirred at 85°C for 4 hours. After cooling, the precipitate was filtered off, washed with dry acetonitrile and dried *in vacuo* to give the title compound **Ex 1** as a pale-yellow powder (5.41 g, 18.2 mmol, 95%). ^{1}H NMR (300 MHz, D_2O): δ 2.10 (s, 3H), 2.90 (s, 6H), 7.29 (d, 1H), 7.39 (s, 1H), 7.83 (d, 1H); Melting point: 141-143°C (uncorrected).

Example 2

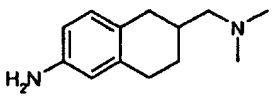
***N*-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide, hydrochloride**



To a suspension of the compound of **Ex 1** (5.4 g, 18 mmol) in acetic acid (100 ml) was added 10% palladium on carbon (1.2 g, 20% w/w). The reaction mixture was stirred at 55°C under a hydrogen atmosphere for 35 hours. The catalyst was filtered off through a celite pad and the filtrate was concentrated *in vacuo* to give a yellow semi-solid, which was triturated with ethyl acetate. The solid was filtered off, washed with further ethyl acetate and dried *in vacuo* to give a pale-yellow solid which was recrystallised in hot methanol to yield the title compound **Ex 2** as a white crystalline solid (1.97 g, 6.96 mmol, 39%). 1H NMR (300 MHz, D2O): δ 2.04 (s, 3H), 2.83 (s, 6H), 7.04 (m, 3H); Melting point: 229 - 230°C (uncorrected).

Example 3

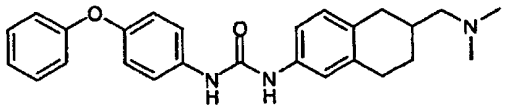
6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamine



A solution of the compound of **Ex 2** (1.97 g, 6.96 mmol) in 2M aqueous HCl (35 ml) was refluxed overnight. The solvent was removed *in vacuo* to yield a white solid which was basified with a 2M aqueous Na_2CO_3 solution and extracted with dichloromethane (3 x 80 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **Ex 3** as an orange-pink oil which solidified upon standing (1.37 g, 6.68 mmol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 6H), 3.50 (bs, 2H), 6.48 (m, 2H), 6.90 (d, 1H); Melting point: 42.5-44.5°C (uncorrected).

Example 4

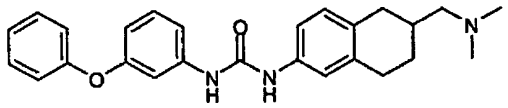
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea



To a solution of the compound of **Ex 3** (0.020 g, 0.098 mmol) in dry dichloromethane (2 ml) was added, under an argon atmosphere, 4-phenoxyphenylisocyanate (0.020 ml, 0.117 mmol). After stirring for 2 hours, PS-trisamine (0.029 mg, 3.38 mmol/g, 0.098 mmol) was added and the reaction mixture was stirred overnight, leading to the formation of a white precipitate. Methanol was added to dissolve the precipitate. PS-trisamine was filtered off and washed with dichloromethane. The filtrate was concentrated *in vacuo* to yield the title compound **Ex 4** as a white solid (0.036 g, 0.087 mmol, 89%). ^{1}H NMR (300 MHz, DMSO-D_6): δ 2.14 (s, 6H), 6.80-7.50 (m, 12H), 8.44 (s, 1H), 8.60 (s, 1H); Melting point: 185-186.5°C (uncorrected).

Example 5

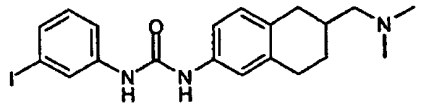
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-phenoxy-phenyl)-urea



The title compound **Ex 5** was obtained by carrying out the same procedure as in Example 4, using the compound of Ex 3 and commercially available 3-phenoxyphenylisocyanate. ^{1}H NMR (300 MHz, DMSO-D_6): δ 2.15 (s, 6H), 6.58-7.40 (m, 12H), 8.46 (s, 1H), 8.74 (s, 1H).

Example 6

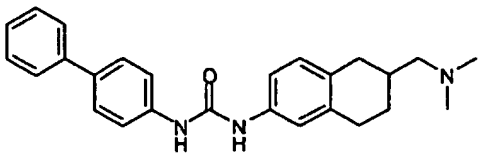
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(3-iodo-phenyl)-urea



The title compound **Ex 6** was obtained by carrying out the same procedure as in Example 4, using the compound of **Ex 3** and commercially available 3-iodophenylisocyanate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 6H), 6.88-7.60 (m, 7H).

Example 7

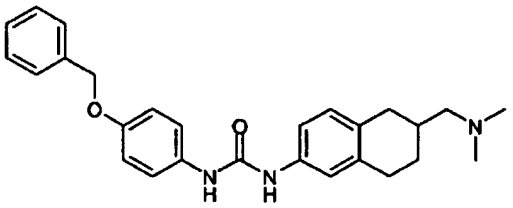
1-Biphenyl-4-yl-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea



The title compound **Ex 7** was obtained by carrying out the same procedure as in Example 4, using the compound of **Ex 3** and commercially available 4-biphenylisocyanate. ^{1}H NMR (300 MHz, DMSO-D_6): δ 2.15 (s, 6H), 6.95-7.60 (m, 12H), 8.53 (s, 1H), 8.73 (s, 1H).

Example 8

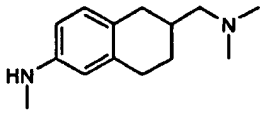
1-(4-Benzyloxy-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea



The title compound **Ex 8** was obtained by carrying out the same procedure as in Example 4, using the compound of **Ex 3** and commercially available 4-benzyloxyphenylisocyanate. ^{1}H NMR (300 MHz, DMSO-D_6): δ 2.13 (s, 6H), 5.05 (s, 2H), 6.91-7.45 (m, 12H), 8.37 (d, 2H).

Example 9

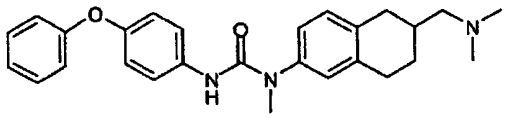
6-(Dimethylaminomethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl-N-methylamine



To a solution of **Ex 3** (18 mg, 0.09 mmol) in dry methanol (2 ml) were added sodium methoxide (30 mg, 0.56 mmol) and paraformaldehyde (13 mg, 0.15 mmol). The reaction mixture was stirred at 40°C 16 hours. The reaction mixture was cooled to room temperature whereupon sodium borohydride (9 mg, 0.23 mmol) was added and the reaction mixture was continuously stirred at 50°C over night. The reaction mixture was concentrated in vacuo to give a solid residue which was triturated with diethyl ether and $NaHCO_3$ (aq). The water phase was further extracted with diethyl ether (2 x 20 mL) and the combined organic phased was dried over $NaSO_4$, filtered and evaporated. The crude product was purified by chromatography (silica, dichloromethane/methanol/ammoniak, 100:10:1) giving 8 mg (39%) of the title compound.^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 6H), 2.81 (s, 3H), 6.33 (d, 1H), 6.43 (dd, 1H), 6.92 (d, 1H).

Example 10

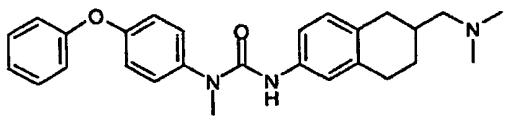
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1-methyl-3-(4-phenoxy-phenyl)-urea



The title compound **Ex 10** was obtained by carrying out the same procedure as in Example 4, using **Ex 9** and commercially available 4-benzyloxyphenylisocyanate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (s, 3H), 8.02 (s, 1H).

Example 11

3-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1-methyl-1-(4-phenoxy-phenyl)-urea

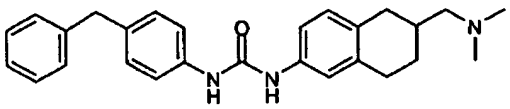


To a cooled (0°C) solution of phosgene (20% phosgene solution in toluene, 0.25 ml, 0.5 mmol) in dry toluene (5 ml) was slowly added a pre-cooled (0°C) solution of N-methyl 4-phenoxyphenyl aniline (100 mg, 0.5 mmol) and diisopropylethylamine (0.17 ml, 1 mmol) in dry toluene (5 ml). To this solution was then added, after stirring for a further 10 minutes, **Ex 3** (51.5 mg, 0.25 mmol) in one portion. The reaction mixture was stirred at 0°C for 10 minutes following the addition of **Ex 3**. The reaction mixture was then allowed to stir at room temperature for 18 hours. Solvent was removed *in vacuo*. The residue was

dissolved in dichloromethane, washed with sat.aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The brown oil was purified over silica gel chromatography (CH_2Cl_2/MeOH/NH_3: 90/9/1) to give the title compound **Ex 11** (31 mg, 0.07mmol, 29%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 2.4 (s, 6H), 3.32 (s, 3H), 6.14 (s, 1H), 6.97 – 7.43 (m, 12H).

Example 12

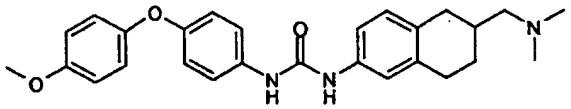
1-(4-Benzyl-phenyl)-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-urea



The title compound **Ex 12** was obtained by carrying out the same procedure as in Example 4, using **Ex 3** and commercially available 4-benzylphenylisocyanate. ^1H NMR (300 MHz, $CDCl_3$): δ2.21 (s, 6H), 3.85 (s, 2H), 6.87 - 7.33 (m, 14H).

Example 13

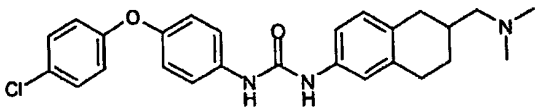
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphtalen-2-yl)-3-[4-(methoxy-phenoxy)-phenyl]-urea



To a suspension of 4-(4-methoxyphenoxy)-benzoic acid (105 mg, 0.43 mmol) in dry toluene (5 ml) were successively added triethylamine (0.060 ml, 0.43 mmol) and diphenylphosphorylazide (0.092 ml, 0.43 mmol). The resulting homogeneous reaction mixture was heated to reflux for 2 hours. After cooling, **Ex 3** (44 mg, 0.215 mmol) was added in one portion and the reaction was then heated at 40°C overnight under vigorous stirring. PS-trisamine (98 mg,4.36 mmol/g, 0.43 mmol) and dry dichloromethane (5 ml) were added and stirring was continued for a further 24 hours. The resin was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with methanol and purified using SCX loaded column from Argonaut to give the title compound **Ex 13** as a white solid (30 mg, 0.067 mmol, 30%). ^1H NMR (300 MHz, $CDCl_3$): δ: 2.24 (s, 6H), 3.79 (s, 3H), 6.87 - 7.33 (m, 14H), 6.42 (s, 1H), 6.52 (s, 1H), 6.85 – 7.25 (m, 11H).

Example 14

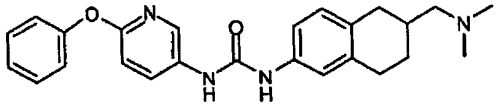
1-[4-(4-Chloro-phenoxy)-phenyl]-3-(6-dimethylaminomethyl-5,6,7,8-tetrahydro-naphtalen-2-yl)-urea



The title compound **Ex 14** was obtained by carrying out the same procedure as in Example 13, using **Ex 3** and commercially available 4-(4-chlorophenoxy)benzoic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ2.5 (s, 6H), 6.85 - 7.4 (m, 11H), 7.5 (s, 1H), 7.6 (s, 1H).

Example 15

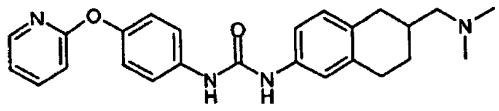
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(6-phenoxy-pyridin-3-yl)-urea



The title compound **Ex 15** was obtained by carrying out the same procedure as in Example 13, using **Ex 3** and commercially available 6-phenoxynicotinic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 6.68 (d, 1H), 6.84 – 7.34 (m, 8H), 7.73 (dd, 1H), 7.99 (d, 1H), 8.04 (s, 1H), 8.38 (s, 1H).

Example 16

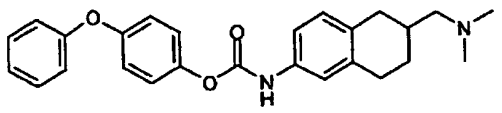
1-(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphtalen-2-yl)-3-[4-(pyridine-2-yloxy)-phenyl]-urea



The title compound **Ex 16** was obtained by carrying out the same procedure as in Example 13, using **Ex 3** and 4-(Pyridin-2-yloxy)-benzoic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 6H), 6.71 (s, 1H), 6.85 – 7.3 (m, 10H), 7.65 (m, 1H), 8.15 (m, 1H).

Example 17

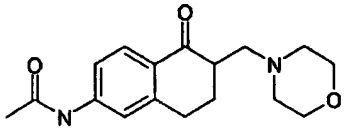
(6-Dimethylaminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-carbamic acid 4-phenoxy-phenyl ester



The title compound **Ex 17** was obtained by carrying out the same procedure as in Example 11, using **Ex 3** and commercially available 4-phenoxyphenol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 6H), 7 – 7.4 (m, 13H).

Example 18

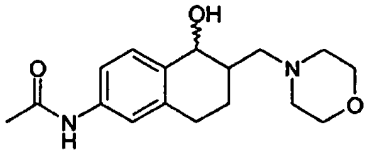
N-(6-Morpholin-4-ylmethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide



To morpholine hydrochloride (1.7g, 19.6 mmol) was added formaldehyde (1.6 mL, 37% w/v, 19.6 mmol) and the solution was allowed to stand for 1h before slow addition to acetic anhydride (9.5 mL) Rapid addition leads to excessive exotherm. The mixture was then heated gently until complete solution was formed before the addition of *N*-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide (2g, 9.8 mmol) and the solution was refluxed for 2h. After cooling, the volatiles were removed *in vacuo*. The oily residue was triturated with acetone leading to the precipitation of the title compound **Ex 18** as its hydrochloride salt (1.46 g, 50%). ^{1}H NMR ($CDCl_3$) δ: 7.98 (1H, d, *J* 8.5), 7.75-7.69 (2H, m), 7.24 (1H, dd, *J* 8.5, 2.2), 3.68-3.64 (4H, m), 2.85-1.74 (11H, m).

Example 19

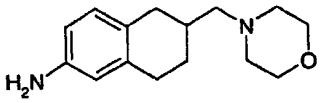
N-(5-Hydroxy-6-morpholin-4-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide



To a solution of amine **Ex 18** (1.46 g, 4.8 mmol) in dichloromethane (100 mL) at -78°C was added a solution of DiBAl (9.6 mL, 1 M, 9.6 mmol, in dichloromethane). The solution was allowed to stir overnight with warming to ambient temperature. The reaction was quenched by the addition of methanol (1 mL) followed by the addition of water (1 mL). The resulting mixture was then added to a vigorously stirred, saturated solution of Rochelle's salts. Stirring continued for 3h before the mixture was extracted with dichloromethane (3 x 50 mL). The combined organics were then washed with water (50 mL) and brine (50 mL). The oily residue was purified by column chromatography eluting with a methanol dichloromethane gradient to yield the title compound **Ex 19** (259 mg, 18%). ^{1}H NMR ($CDCl_3$) δ: 7.58 (1H, s), 7.52 (1H, d, *J* 8.5), 7.43 (1H, s), 7.23 (1H, d, *J* 8.5), 4.81 (1H, d, *J* 3.9), 3.72 (4H, m), 2.78-1.64 (11H, m).

Example 20

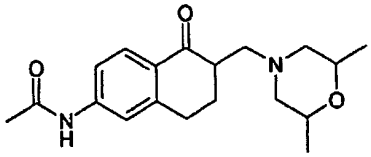
6-Morpholin-4-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamine



To **Ex 19** (259 mg, 0.85 mmol) was added hydrochloric acid (2M, 4.25 mL, 8.5 mmol) and the solution was then heated to 95°C for 16h. The reaction mixture was then cooled and basified with sodium hydroxide and then extracted with dichloromethane (3 x 5 mL). The organics were then filtered through a phase separation membrane before the volatiles were removed *in vacuo*. The crude product was purified by column chromatography eluting with a methanol dichloromethane gradient to give 6-Morpholin-4-ylmethyl-7,8-dihydro-naphthalen-2-ylamine (100 mg, 47 %). To 6-Morpholin-4-ylmethyl-7,8-dihydro-naphthalen-2-ylamine (100 mg, 0.4 mmol) was added subsequently methanol (5 mL) and then 10% palladium on carbon (20 mg). The reaction vessel was then sealed and the atmosphere exchanged with nitrogen and then hydrogen and vigorous stiring was maintained for 16h before the being filtered through a celite plug (1 g). The residue was washed with excess methanol and the combined organics were reduced *in vacuo* to give the title compound **Ex 20**. ^{1}H NMR ($CDCl_3$) δ: 6.88 (1H, d), 6.48 (1H, dd), 6.42 (1H, s), 3.75 (4H, m), 2.86-1.85 (12H, m), 1.46-1.30 (1H, m).

Example 21

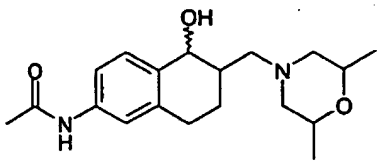
N-[6-(2,6-Dimethyl-morpholin-4-ylmethyl)-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl]-acetamide



The title compound **Ex 21** (1.6 g, 50 %) was obtained by carrying out the same procedure as in Example 18, using commercially available *N*-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide and 2,6-Dimethyl-morpholine hydrochloride.
^{1}H NMR (D_2O) δ: 7.85 (1H, d, *J* 8.0), 7.40 (1H, s), 7.33 (1H, m), 4.50-1.82 (16H, m), 1.28 (6H, m)

Example 22

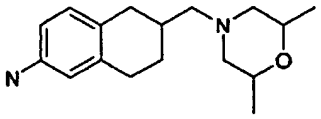
N-[6-(2,6-Dimethyl-morpholin-4-ylmethyl)-5-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl]-acetamide



The title compound **Ex 22** (327 mg, 20%) was obtained by carrying out the same procedure as in Example 19, using **Ex 21**. ^{1}H NMR ($CDCl_3$) δ: 7.55-7.47 (2H, m), 7.39 (1H, s), 7.19 (1H, d), 4.81 (1H, d, *J* 3.9), 3.65 (2H, m), 3.10-2.18 (8H, m), 2.16 (3H, s), 1.84-1.66 (3H, m), 1.18 (3H, d), 1.12 (3H, d).

Example 23

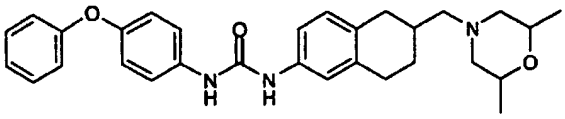
6-(2,6-Dimethyl-morpholin-4-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-ylamine



The title compound **Ex 23** (48 mg, 17%) was obtained by carrying out the same procedure as in Example 20, using **Ex 22**. ^{1}H NMR ($CDCl_3$) δ: 6.82 (1H, d), 6.44 (2H, m), 6.25 (1H, s), 4.10-3.98 (2H, m), 3.72-3.50 (2H, br s), 3.08-2.12 (10H, m), 1.24 (6H, d).

Example 24

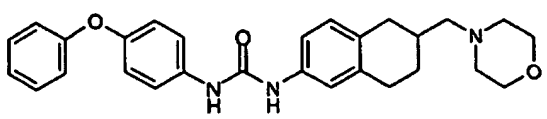
1-[6-(2,6-Dimethyl-morpholin-4-ylmethyl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(4-phenoxy-phenyl)-urea



The title compound **Ex 24** (4 mg, 5 %) was obtained by carrying out the same procedure as in Example 25, using **Ex 23** and commercially available 4-phenoxyphenylisocyanate. ^{1}H NMR ($CDCl_3$) δ: 7.38-7.27 (5H, m), 7.12-6.95 (7H, m), 6.67 (1H, br s), 6.51 (1H, br s), 4.12-3.98 (2H, m), 2.95-1.91 (12H, m), 1.45-1.35 (1H, m), 1.26 (6H, d).

Example 25

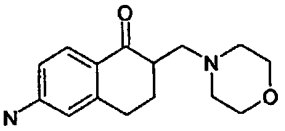
1-(6-Morpholin-4-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-phenoxy-phenyl)-urea



To a solution of **Ex20** (15 mg, 0.06 mmol) in dichloromethane (1 mL) stirred at ambient temperature under argon atmosphere was added 4-phenoxyphenylisocyanate (19 mg, 0.09 mmol). Stirring was continued for 16h before the product was isolated by direct addition of the reaction mixture to SCX column. Impurities were removed by elution with methanol (20 mL) before the elution of product urea with 5% ammonia in methanol (10 mL). Removal of volatiles *in vacuo* to give title compound **Ex 25** (6 mg, 22%). ^{1}H NMR ($CDCl_3$) δ:7.38-7.24 (6H, m), 7.12-6.91 (8H, m), 6.70 (1H, br s), 6.60 (1H, br s), 6.76 (4H, m), 6.91-1.30 (13H, m).

Example 26

6-Amino-2-morpholin-4-ylmethyl-3,4-dihydro-2H-naphthalen-1-one

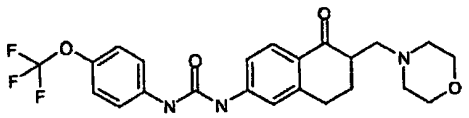


The title compound **Ex 26** was obtained by carrying out the same procedure as in Example 3, using **Ex 18.**

^{1}H NMR ($CDCl_3$) δ: 6.89 (1H, d, *J* 7.8), 6.48 (1H, d, *J* 7.8), 6.43 (1H, s), 3.75 (4H, m), 3.60-3.30 (2H, br s), 2.70-1.20 (11H, m).

Example 27

1-(6-Morpholin-4-ylmethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-(4-trifluoromethoxy-phenyl)-urea

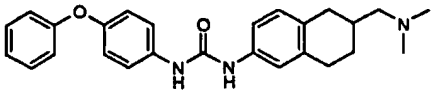
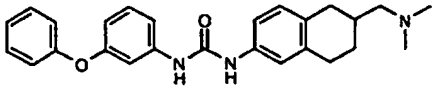
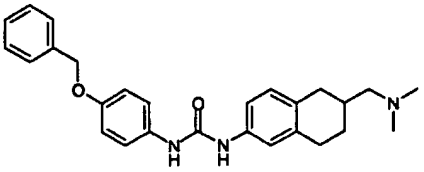
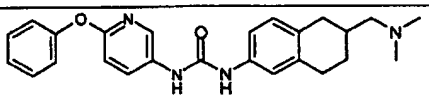
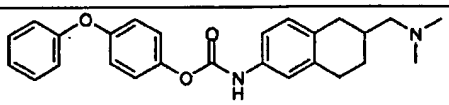
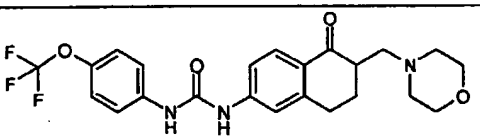


The title compound **Ex 27** was obtained by carrying out the same procedure as in Example 4, using **Ex 26** and commercially available trifluoromethoxyphenylisocyanate. ^{1}H NMR ($CDCl_3$) δ: 7.40-6.84 (7H, m), 3.76 (4H, m), 2.94-2.18 (3H, m), 2.48 (4H, m), 2.30 (1H, d, *J* 8.0), 1.95 (2H, m), 1.33 (1H, m).

Example 28

***In vitro* test of selected compounds according to the invention**

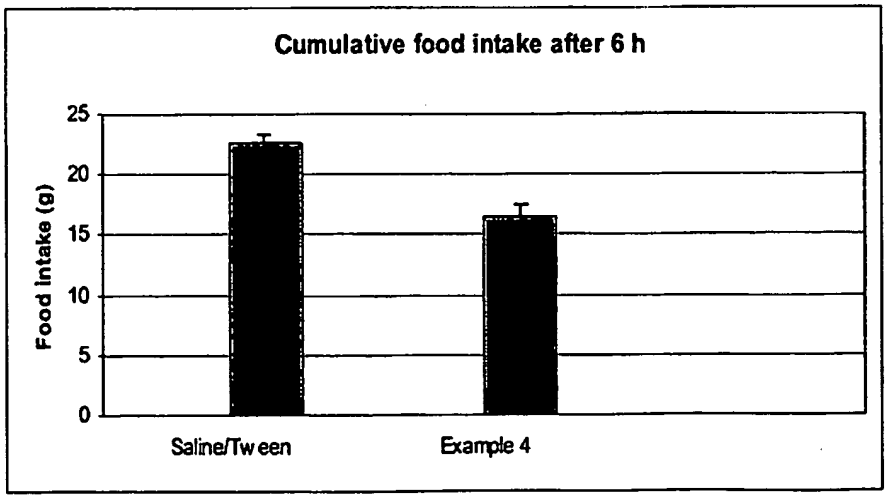
Compound	Example	Receptor binding	IP3 IC_{50} μM

		IC_{50} µM	
	Ex 4	0.010	0.048
	Ex 5	0.23	6.2
	Ex 8	0.093	0.36
	Ex 15	0.037	0.08
	Ex 17	0.055	0.9
	Ex 27	0.056	0.23

Example 29

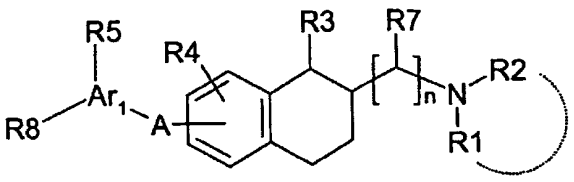
***In vivo* tests of compounds according to the invention**

The following results were obtained on reduction in food intake.

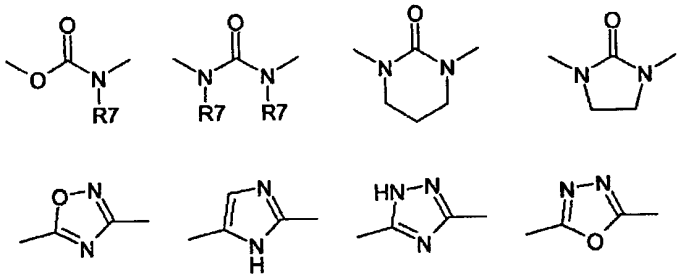


CLAIMS

1. A compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of:



and, wherein the linker may be attached *via* either of the two free bonds to the Ar_1 group;

and R7 is the same or different and is hydrogen or a straight or branched C_1-C_6 alkyl or alkenyl group;

Ar_1 is an aryl or heteroaryl group such as, e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 and R2 are the same or different and selected from hydrogen, straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms, cycloalkyl groups with 3-7 carbon atoms, alkylcycloalkyl groups with 4-9 carbon atoms, alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine, alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, -$CONH_2$, -CONHAlk, $CONAlk_2$, aryl, substituted aryl, benzyl, or substituted benzyl groups;

R1 and R2 may optionally be linked to each other, when possible, as indicated in Formula I, and oxygen or nitrogen atoms may be inserted into the chain or ring in a chemically stable position,

both of R1 and R2 are preferably not hydrogen;

R3 is a hydrogen atom, Alk-, Alk-O-, hydroxy or keto group;

R4 and R5 may be the same or different selected from hydrogen, halogen atoms, alkoxy groups (Alk-O-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

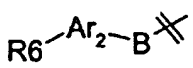
Alk is the same or a different alkyl, alkenyl or alkynyl group;

more than one R5 group, same or different, may be present on Ar_1; when more than one R5 group or one or more R5 and one R8 group are present they could be connected to each other to form rings;

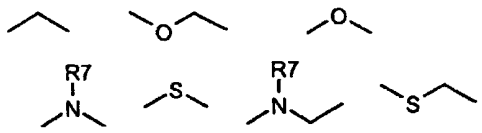
n is 1 or 2;

R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, heteroaryloxyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr, -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -SCH_3, -CF_3, -OCF_3, -SCF_3

or R8 has the structure



in which B is a non-rigid connecting moiety selected from the group consisting of



which may be attached *via* either of the two free bonds to the Ar_1 group

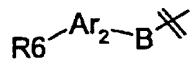
and the -B- moiety is not placed *ortho*- to the -A- moiety;

Ar_2 is an aryl or heteroaryl group such as, *e.g.* phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R6 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

more than one R6 group, same or different, may be present on Ar_2; when more than one R6 group is present they could be connected to each other, directly or with a suitable connecting moiety, to form rings.

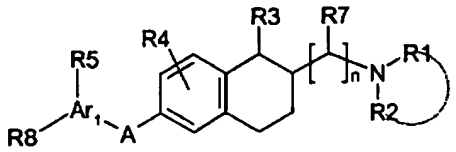
2. A compound according to claim 1, wherein R8 has the structure



and B, Ar_2 and R6 are as defined in claim 1.

3. A compound according to claim 1, wherein R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, heteroaryloxyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr, -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -SCH_3, -CF_3, -OCF_3, -SCF_3.

4. A compound according to any of the preceding claims having the following structure (Formula Ia)

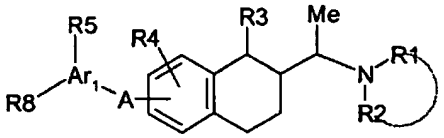


wherein Ar_1, A, R1, R2, R3, R4, R5, R7 and R8 are as defined in claim 1.

5. A compound according to any of the preceding claims, wherein n is 1.

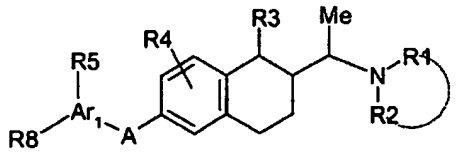
6. A compound according to claim 5, wherein n is 1 and R7 is hydrogen.

7. A compound according to claim 5, wherein the structure (Formula II) is



and wherein Ar_1, A, R1, R2, R3, R4, R5 and R8 are as defined in claim 1.

8. A compound according to claim 7 having the following structure (Formula IIa)



wherein Ar_1, A, R1, R2, R3, R4, R5 and R8 are as defined in claim 1.

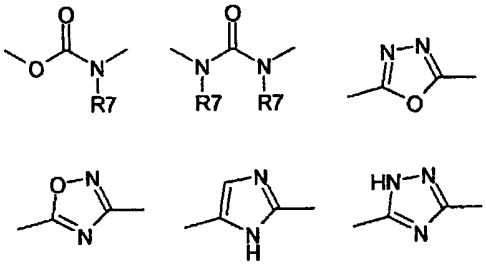
9. A compound according to any of the preceding claims, wherein Ar_1 is aryl or heteroaryl groups such as, e.g. phenyl, pyridine, and thiophene.

10. A compound according to any of the preceding claims, wherein R3 is hydrogen.

11. A compound according to any of the claims, wherein R4 is hydrogen.

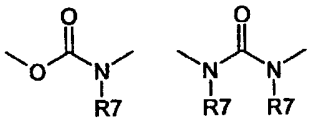
12. A compound according to any of the preceding claims, wherein R3 and R4 both are hydrogen.

13. A compound according to any of the preceding claims, wherein A is selected from the group consisting of:



and R7 is defined as in claim 1.

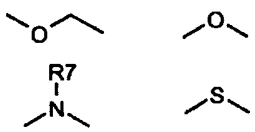
14. A compound according to any of the preceding claims, wherein A is selected from the group consisting of:



and R7 is defined as in claim 1.

15. A compound according to claim 14, wherein at least one R7 on the connecting moiety A is not hydrogen.

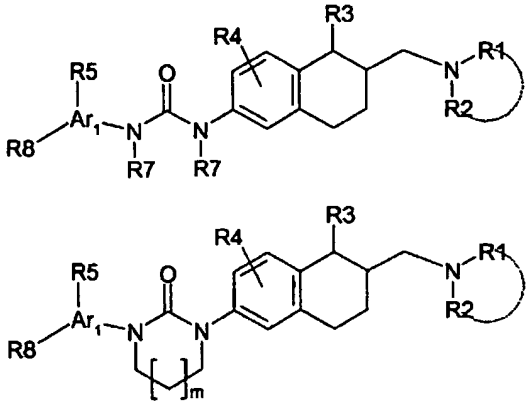
16. A compound according to any of the preceding claims, wherein B is selected from the group consisting of:



and R7 is as defined in claim 1.

17. A compound according to any of the preceding claims, wherein B is selected from the group consisting of:

18. A compound according to any of claims 1-6, 9-17 having one of formulas



and one of R7 being hydrogen and m being 0 or 1

19. A compound according to any of the preceding claims, wherein Ar_1 is an aryl, heterocyclyl or heteroaryl group such as phenyl, pyridine and thiophene, and n is 1.

20. A compound according to claim 19, wherein R3 is hydrogen.

21. A compound according to claim 19, wherein R4 is hydrogen.

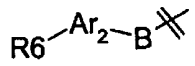
22. A compound according to claim 19, wherein R3 and R4 are both hydrogen.

23. A compound according any of claims 1, 3-22, wherein R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -$CONAlk_2$, -NHCO-Alk, -CO-Alk, -CF_3, -OCF_3, -SCF_3, -SCH_3.

24. A compound according to any of claims 1, 3-22, wherein R8 is aryl groups (Ar), heterocyclyl groups, heteroaryl groups, alkylaryl groups, alkylheteroaryl groups,

alkylheterocyclyl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), -CONHAr, -NHCO-Ar, or -CO-Ar.

25. A compound according to any of claims 1-2, 4-22, wherein R8 has the structure



and Ar_1 and Ar_2 are the same or different aryl or heteroaryl groups such as phenyl, pyridine, and thiophene and n is 1.

26. A compound according to claim 25, wherein R3 is hydrogen.

27. A compound according to claim 25, wherein R4 is hydrogen.

28. A compound according to claim 25, wherein R3 and R4 both are hydrogen.

29. A compound according to any of the preceding claims, wherein R1 and R2 are alkyl, alkenyl or cycloalkyl groups or joined in a morpholino, pyrrolidino or piperidino.

30. A compound according to any of claims 1-28, wherein R1 and R2 are H.

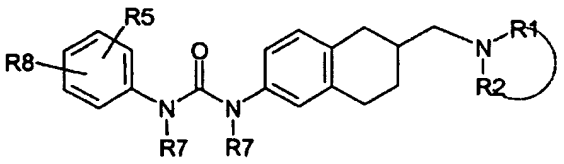
31. A compound according to any of the preceding claims, wherein Ar1 is an aryl or heteroaryl group

32. A compound according to any of the preceding claims, wherein Ar1 is a phenyl group.

33. A compound according to any of claims 1-2, 4-22, 25-32, wherein Ar2 is a phenyl group.

34. A compound according to claim 32 or 33, wherein Ar1 and Ar2 are a phenyl group.

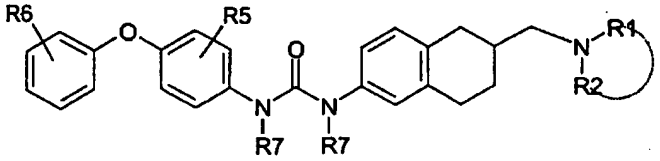
35. A compound according to any of claims 4-6, 9-34 having the structure



and one of R7 being hydrogen.

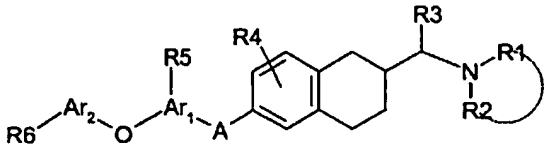
36. A compound according to any of claims 1, 2, 4-22, 25-34, wherein -B- is an ether linkage –O-.

37. A compound according to claim 36 having the structure

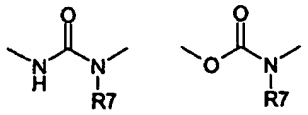


and one of R7 being hydrogen.

38. A compound according to claim 36 with the following structure



wherein –A- is a linker selected from



and R1, R2, R3, R4, R5, R6 and R7 are as defined in any of the preceding claims.

39. A compound according to claim 38, wherein R3 is hydrogen.

40. A compound according to claim 38 or 39, wherein R1 and R3 are hydrogen.

41. A compound according to any of claims 38-40, wherein R1 and R2 are hydrogen and R3 is methyl.

42. A compound according to claim 38 or 39, wherein R1 and R2 are Alk.

43. A compound according to any of claims 38-42, wherein Ar_1 and Ar_2 are the same or different aryl or heteroaryl groups such as phenyl, pyridine, and thiophene.

44. A compound according to any of claims 38-44, wherein R4 is hydrogen.

45. A compound according to any of claims 38-44, wherein Ar_1 and Ar_2 are phenyl groups.

46. A compound according to any of the preceding claims in amorphous or crystalline form.

47. A compound according to any of the preceding claims in racemic or enantiomeric form.

48. A compound according to any of the preceding claims in the form of a physiologically acceptable salt, complex, solvate or prodrug thereof.

49. A compound according to any of the preceding claims for use in medicine.

50. A compound according to any of the preceding claims, which is an agent for preventing or treating diseases caused by or involving a melanin-concentrating hormone.

51. A compound according to any of the preceding claims, which modulates the activity of a MCH receptor.

52. A compound according to any of the preceding claims, which has antagonistic activity against a MCH receptor.

53. A compound according to any of claims 1-51, which has agonistic, inverse agonistic or allosteric activity against a MCH receptor.

54. A compound according to any of the preceding claims, wherein the MCH receptor has at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequence CTLITAMDAN or CTIITSLDTC

55. A compound according to any of the preceding claims, wherein the MCH receptor comprises the amino acid sequence CTLITAMDAN or CTIITSLDTC.

56. A compound according to any of the preceding claims, wherein the MCH receptor is a MCH1 or MCH2 receptor.

57. A compound according to any of the preceding claims, wherein the MCH receptor is a MCH1 receptor.

58. A compound according to any of the preceding claims, wherein the MCH receptor is a mammalian such as human receptor.

59. A compound according to any of the preceding claims, which is an agent for preventing or treating feeding disorders.

60. A compound according to any of claims 1-52 or 54-59, which is an agent for reducing body mass.

61. A compound according to any of claims 1-52 or 54-60, which is an agent for preventing or treating Syndrome X (metabolic syndrome), or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension.

62. A compound according to any of claims 1-52 or 54-61, which is an agent for preventing or treating Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM).

63. A compound according to any of claims 1-52 or 64-62, which is an agent for preventing or treating bulimia, obesity and/or bulimia nervosa.

64. A compound according to any of claims 1-58, which is an antidepressant and/or anti-anxiety agent.

65. A cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to any of claims 1-52 or 54-63.

66. A method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-64.

67. A method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-63.

68. A method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-63.

69. A method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-52 or 54-63.

70. A method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-52 or 54-63.

71. A method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-52 or 54-63.

72. A method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-52 or 54-63.

73. A method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-58 or 64.

74. A pharmaceutical composition comprising a compound according to any of the claims 1-64 or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

75. A pharmaceutical composition according to claim 74, wherein the compound is present in the form of a physiologically acceptable salt such as a salt formed between the compound and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_5 salt, or a salt formed between the compound and an organic acid such as organic acids like e.g. H_2CO_3, acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, citric acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

76. A pharmaceutical composition according to claim 74 or 75 for enteral and/or parenteral use.

77. A pharmaceutical composition according to claim 74 or 75 for oral, buccal, rectal, nasal, topical, vaginal or ocular use.

78. A pharmaceutical composition according to any of claims 74-77 in the form of a solid, semi-solid or fluid composition.

79. A pharmaceutical composition according to claim 78 in solid form, wherein the composition is in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, or particulate material.

80. A pharmaceutical composition according to claim 78 in semi-solid form, wherein the composition is in the form of a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

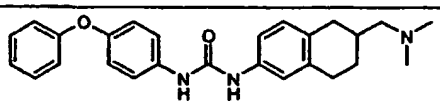
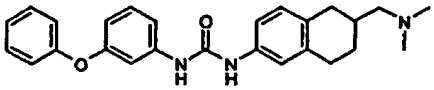
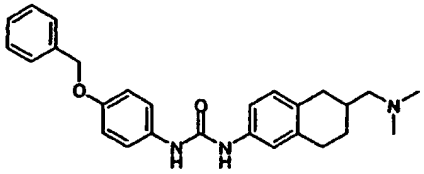
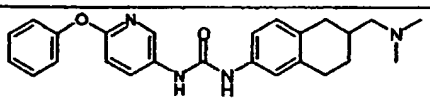
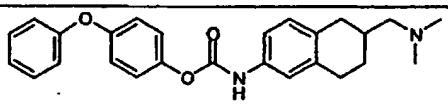
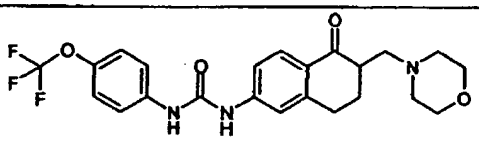
81. A pharmaceutical composition according to claim 78 in fluid form, wherein the composition is in the form of a solution, an emulsion, a suspension, a dispersion, a liposomal composition, a spray, a mixture, or a syrup.

82. A pharmaceutical composition according to any of claims 78-81 comprising a therapeutically effective amount of a compound according to any of claims 1-64.

83. A pharmaceutical composition according to claim 82, wherein the amount is from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

84. Use of a compound according to any of claims 1-52 or 54-63 or a pharmaceutically acceptable salt thereof for the manufacture of a cosmetic composition for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto.

85. Use of a compound according to any of claims 1-64 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for i) the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, ii) the treatment and/or prophylaxis of diseases caused by feeding disorders, iii) modifying the feeding behaviour of a mammal, iv) the reduction of body mass, v) the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, or vi) the treatment and/or prophylaxis of depression and/or anxiety.

		IC_{50} µM	
	Ex 4	0.010	0.048
	Ex 5	0.23	6.2
	Ex 8	0.093	0.36
	Ex 15	0.037	0.08
	Ex 17	0.055	0.9
	Ex 27	0.056	0.23

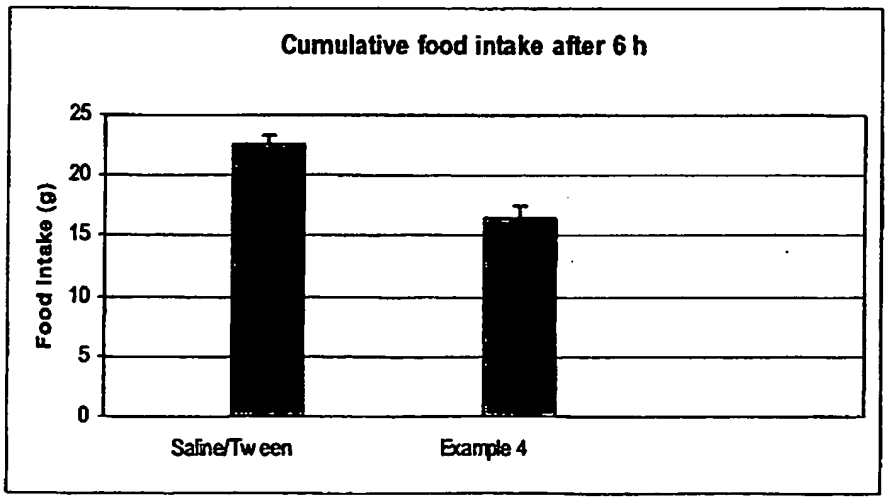


Fig. 1

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/DK 03/00233

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/28 C07C237/48 A61K31/167 A61K31/17 A61P3/04
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1 X	WO 01 21577 A (ISHIHARA YUJI ;KATO KANEYOSHI (JP); MORI MASAAKI (JP); SHIMOMURA Y) 29 March 2001 (2001-03-29) page 171 -page 173	1-85

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	07. 07. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GÓMEZ LAGERLÖF /EÖ

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00233

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 66-73
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 66-73

Claims 66-73 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

ition on patent family members

Internatl Application No
PCT/UK 03/00233

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0121577 A	29-03-2001	AU 7315700 A	24-04-2001
		CA 2386474 A1	29-03-2001
		EP 1218336 A2	03-07-2002
		WO 0121577 A2	29-03-2001
		JP 2002003370 A	09-01-2002

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